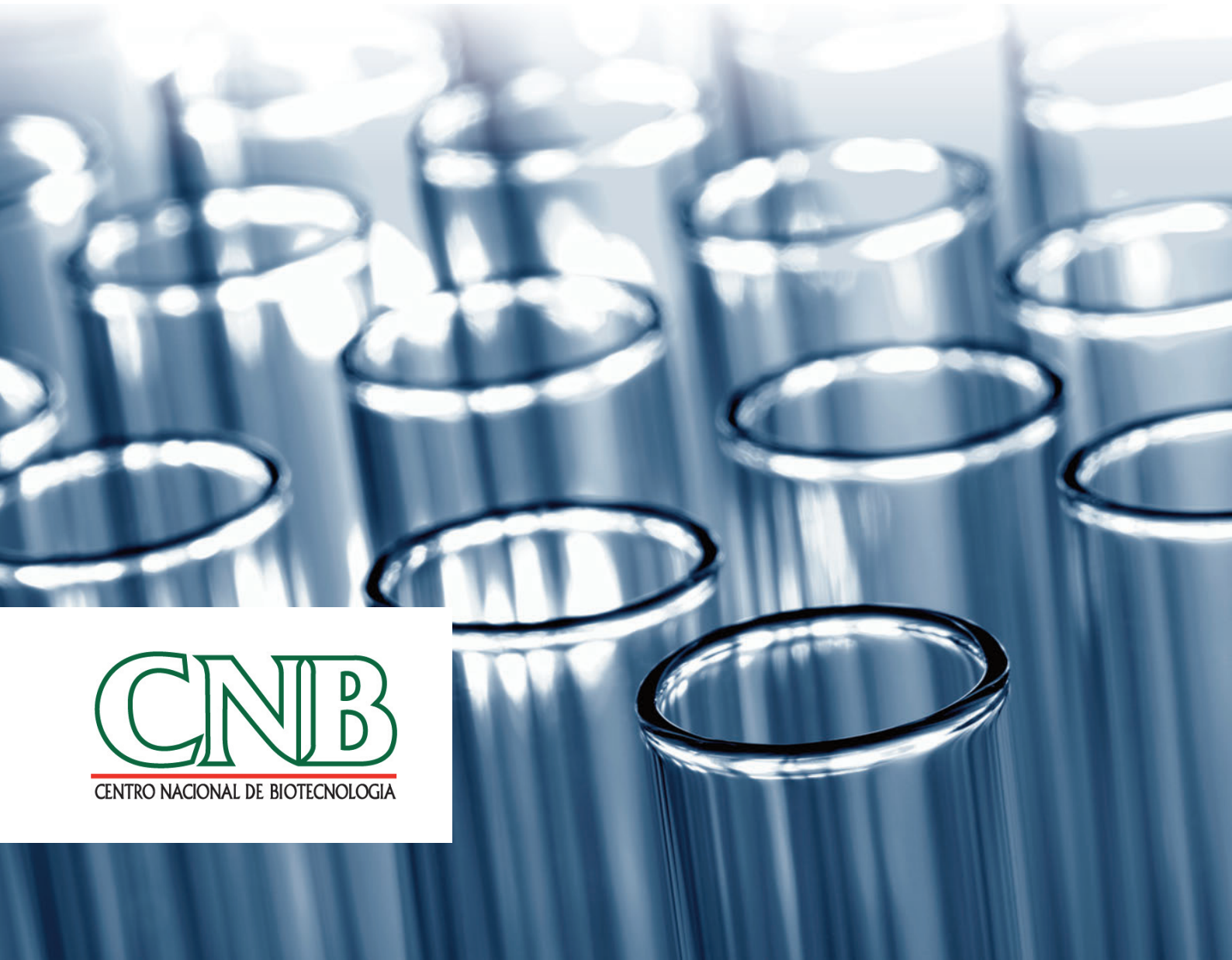
STEM CELLS AND IMMUNITY:

From stem cell biology to tissue mending



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RESEARCH EXCELLENCE ON THE 'HORIZON'

Adjacent Government gives an overview of the work the European Commission, and Horizon 2020 is doing to help fund research in the area of stem cells...

Europe undoubtedly boasts an impressive research base, one that has grown from strength to strength. The support of the European Commission in nurturing and growing Europe's science platform has been significant and has allowed risks to be taken. Pioneering research continues to steam ahead, bringing Europe closer to becoming a leader in many fields.

The European Commission (EC) has done much to increase innovation and support research within the European Union. Bringing together member states, often with different cultural identities and ethical ideologies, has undoubtedly been challenging at times, but the continued presence of the EC has seen a breaking down of barriers and the disappearance of borders for science progression.

This year, the Commission launched its largest research and innovation programme. Replacing the former Seventh Framework Programme, Horizon 2020 will run for 7 years and expects to deliver more discoveries and pioneering science during the period. With a budget of €80bn over the 7 year period, it is hoped that Europe will continue to develop as a research powerhouse.

Máire Geoghegan-Quinn, European Commissioner for Research, Innovation and Science explained why Horizon 2020 is different from previous programmes and how it will change the European research landscape:

"Horizon 2020 is putting a lot of research money into finding answers to societal challenges. It's challenging all the disciplines to step outside their comfort zones. We don't have neat little boxes [for each scientific area] like we had before, and that's a criticism I suppose in one way by some of the disciplines. Everybody's being asked to do things differently, and that's always challenging."[1]

Pushing the boundaries of research is something the Commissioner is keen to do and she has actively supported cutting edge research during her tenure. One area that gained significant attention from Geoghegan-Quinn is stem cell research.

Stem cells have the ability to rebuild damaged cells and offer a renewable source of cell replacement. Because of this, stem cells have been heralded the future of medicine, offering a very real solution to many diseases and disorders.

Adult and foetal stem cells are only able to develop into specific cells, but embryonic stem cells can become almost any type of cell in the body. For this reason, embryonic stem cells have – and can – play an important role in medicine.

However, the use of human embryonic cells in medicine has been controversial and has raised numerous questions about the ethical implications. Recognising the challenges of this field, the Commission were careful to address the issue of stem cells in the proposal for the regulation of Horizon 2020.

One section of the proposal stated that, "The European Commission does not explicitly solicit the use of human embryonic stem cells. The use of human stem cells, be they adult or embryonic, if any, depends on the judgement of the scientists in view of the objectives they want to achieve and is subject to stringent Ethics Review. No project involving the use of human embryonic stem cells should be funded that does not obtain the necessary

approvals under the law of the Member State concerned. No activity should be funded that is forbidden in all Member States. No activity should be funded in a Member State where such activity is forbidden."[2]

Adhering to the laws of each member state is something that the Commission must remain sensitive to when setting up guidelines for new, controversial research such as with stem cells. The regulation also made it clear that research should not be funded through Horizon 2020 that would "create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer."[3]

Furthermore, the regulation also said that: "The Commission should actively support research aiming at developing alternatives to embryonic stem cells. The recent discovery of induced pluripotent stem cells (iPSCs) has opened up a new avenue for research, over and beyond the opportunities for research on adult and embryonic stem cells that have existed for several years, and has thus offered new hope to patients awaiting treatment. Nevertheless, the Commission should also take due account of the scientific community's interest in all types of stem cell research and, therefore, not favour any one over another, while considering the ethical problems raised by each category of stem cells."[4]

Stem cell research is undoubtedly an exciting and promising field, but one that must be approached carefully and sensitively. However, if stem cell research is allowed to flourish, the future may see numerous diseases treated using stem cell therapy. Previously incurable diseases could be treated by replacing the damaged cells or tissue with new cells.

Horizon 2020 certainly offers much in the way of support for cutting edge research, but what legacy it will achieve remains to be seen. What is clear is that Geoghegan-Quinn and her Commission will tackle the controversial areas, if there is a benefit to society.

"Horizon 2020 won't shy away from policy issues that are at the top of the agenda and that demand a firm evidence base, such as security, migration or climate change. Nor are we ignoring issues concerning the role of science in our society," said Geoghegan-Quinn. "We are addressing difficult and emotive questions such as the use of stem cells. I think that Horizon 2020's approach on this issue shows that we can find balanced solutions at European level that satisfy divergent positions."[5]

[1] http://news.sciencemag.org/europe/2013/12/geoghegan-quinn-surveys-europes-science-horizon

[2] http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2012-0427&language=EN

[3] http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2012-0427&language=EN

[4] http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2012-0427&language=EN

[5] http://europa.eu/rapid/press-release_SPEECH-14-83_en.htm

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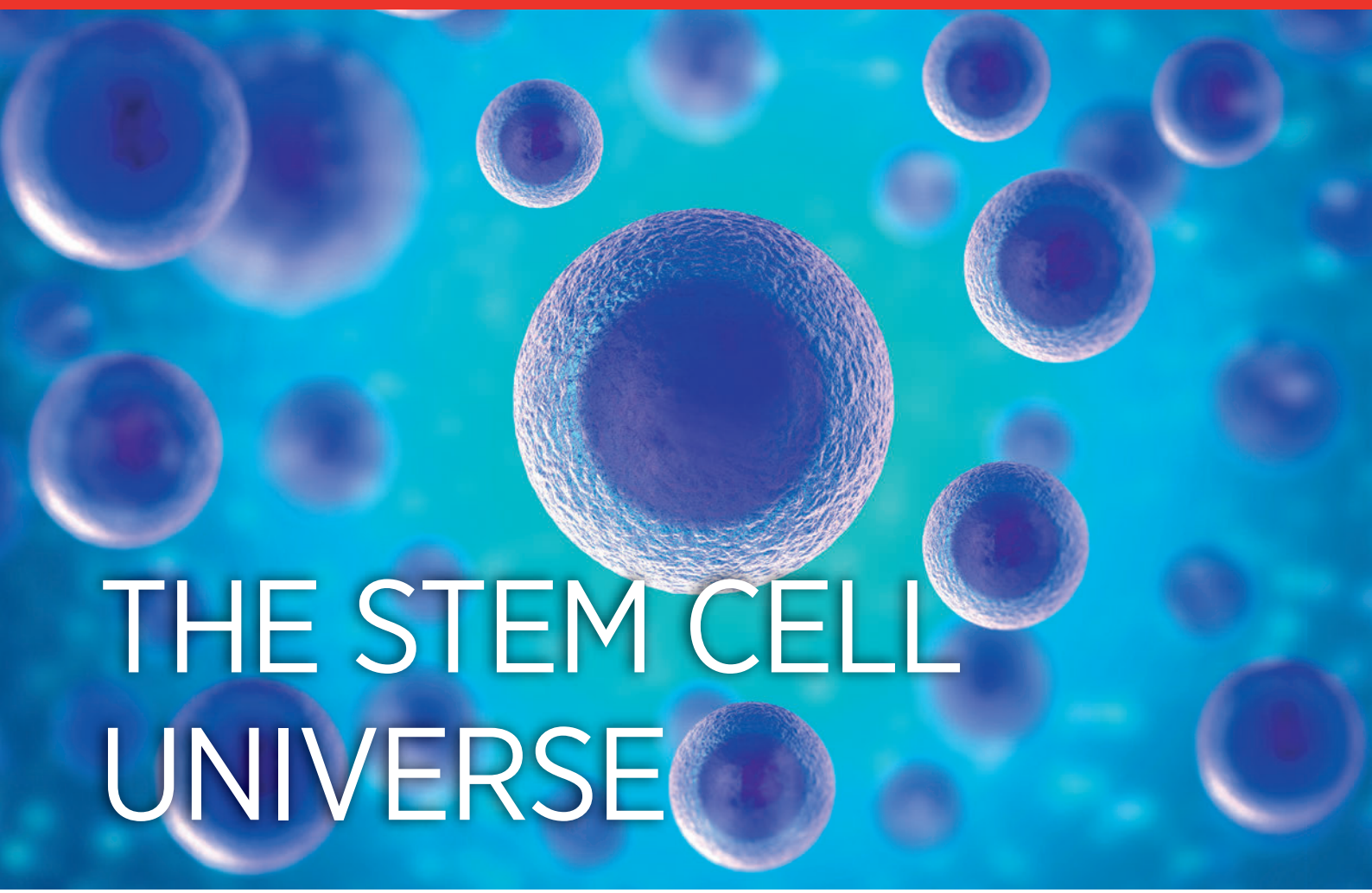

THE STEM CELL UNIVERSE

By Antonio Bernad, Karel van Wely and Carlos Martinez-A

In the last 25 years, tremendous advances have been made in the identification and generation of stem cells (SC) from diverse organisms, generating a wealth of knowledge in various fields from embryology to development. SC not only have the ability to differentiate into several cell types, but are also capable of prolonged self-renewal in an undifferentiated state. SC can be classified according to the range of cell types into which they can differentiate. This property, termed potency, is dictated by progressive hierarchical differentiation; totipotent SC can differentiate into embryonic and extra-embryonic tissues, pluripotent cells can form embryonic tissues (ectoderm, mesoderm and endoderm), and multipotent SC become only a reduced number of cell types. In addition to potency, SC ontogeny is important. Embryonic SC (ESC) are harvested from the inner cell mass of the blastocyst of 5-day-old preimplantation embryos and are pluripotent. Fetal stem cells (from different tissues) are considered multipotent. Most, if not all, organs and adult functional structures harbor adult stem cells (ASC). Finally, umbilical cord tissue is an important, practical source of multipotent stem cells that can be stored for long periods in tissue banks.

Therapeutic application of stem cells is based on a variety of strategies, of which cell replacement therapy is the best-known. The predominant alternative method relies on paracrine effects, in which the transplanted stem cells secrete trophic factors that induce or promote self-repair. There is no universal method, and a specific SC source or determined procedures must be prioritised depending on the pathology or the patient's medical condition.

Despite the expectations that stem cell biology generates, current SC research is driven mainly by regenerative/reparative medicine, which tries to identify conditions useful for replacement of malfunctioning organs in the body. To consolidate the efficiency and safety of new SC therapies, however, a sustained effort that encompasses trial and error will be necessary, as was the case for gene therapy[1]. SC approaches are also being used to generate interesting models for human disease and are currently producing a revolution in the understanding of several human diseases and the creation of physiological testing platforms (even personalised) for screening chemical and molecular drugs and for toxicology.

Embryonic stem cells

ESC are obtained from early stage embryos; they have indefinite self-renewal capacity and can differentiate into cell types derivative of all three germ layers. They provide a powerful research tool for developmental biology, drug screening, disease modeling, and potentially in cell replacement therapy. The ESC concept was established in mice in 1987, and translated to humans[2]. Controlled, efficient differentiation protocols will lead to maximal exploitation of these cells. Their use has ethical considerations associated with

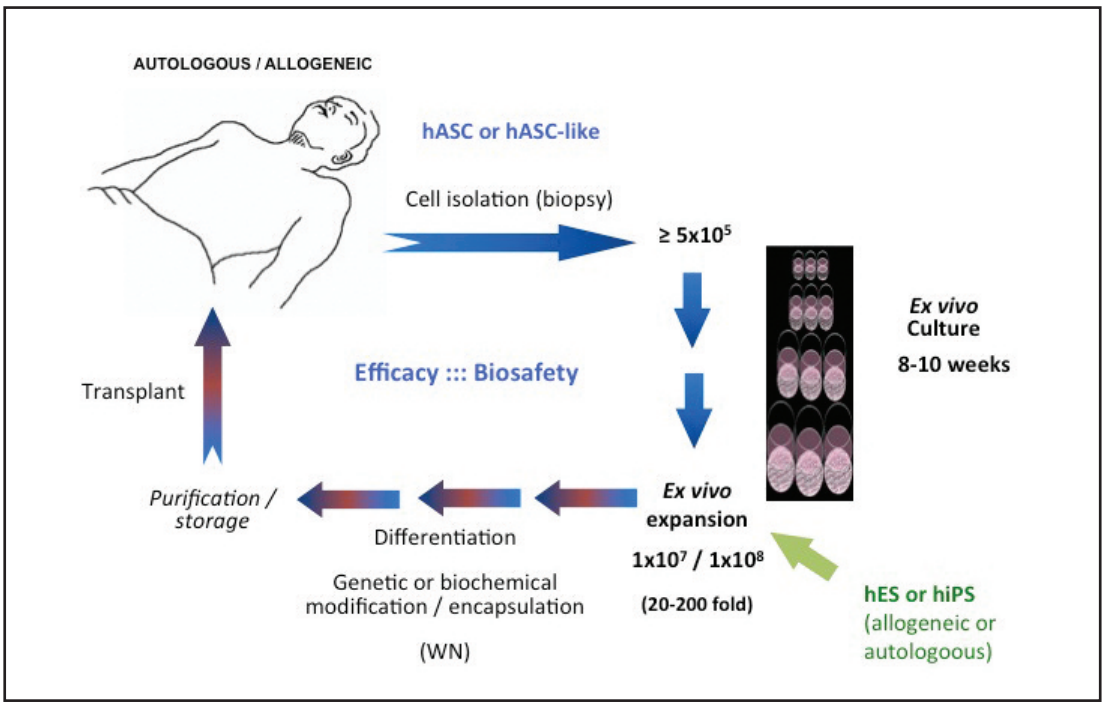

Figure 1. Schematic representation of cell therapy medicines development, using adult (ASC) or embryonic (ES or iPS) cells, for allogeneic or autologous treatments. WN: when necessary or indicated.

the destruction of human embryos to obtain ESC cell lines, and research in the field is controlled in Europe by strict legislation[3].

Yamanaka[4] recently developed revolutionary procedures for obtaining ES-like cells from somatic cells, known as reprogramming. These cells are termed induced pluripotent stem cells (iPS) and show potency comparable to that of ESC. These iPS have immense potential and can be obtained from an adult patient in a reasonable period of time, eliminating most ethical concerns associated with ESC. Procedures to derive specific cell lineages are being developed and show promising results, yielding hematopoietic stem cells (HSC), mesenquimal stem cells (MSC), cardiomyocytes (CS), dendritic cells and dopaminergic neurons. These advances will boost research in replacement therapy, as well as physiological drug screening, toxicology and biosafety studies. Several clinical trials to test the clinical potential of iPS will soon be under way[5].

A more recent and successful approach allows generation of ASC-like cells by partial, guided reprograming of adult somatic cells while avoiding the pluripotent state. This direct reprogramming aims to produce an artificial population with potential similar to that of tissue-resident ASC[6]. When it becomes consolidated, direct reprogramming could prove a decisive aid in many research lines.

Adult stem cells

The cradle of SC therapy was in bone marrow transplant research. This community established and developed central concepts that have since been shown to apply to most ASC systems[7]. These contributions remain relevant more than 40 years after the first descriptions of hematopoietic stem cells (HSC) in the bone marrow, and intense research continues to decipher the laws of HSC regulation and its alteration in hematopoietic pathologies.

Adult stem cells (ASC) are central participants in the repair of most, if not all, host tissues in mature organisms, and the prevention of ASC senescence is critical for tissue homeostasis. ASC have been identified clearly in most mammalian tissues, even in those previously considered fully postmitotic. In the case of cardiac muscle, however, there is a long-standing debate regarding the existence of resident cardiac stem cells or the dedifferentiation of a yet unidentified cardiomyocytic subpopulation. Maintenance of a small population (compartment) of immature cells seems to be the dominant situation in mammals, so it is thought that the heart will adhere to this general rule, in support of slight, but real ASC activity.

Bmi1 expression is reported to have a crucial role in the self-renewal and maintenance of hematopoietic, neural, intestinal, bronchioalveolar, pancreatic, prostate, lung and epithelial SC, as well as in the tongue and in rodent incisors; Bmi1 thus seems to be a general marker for ASC. Bmi1 is one of the main regulators of INK4a/ARF, encoding p16, which in turn is associated with cell senescence and ageing. The effects of p16 activity include not only loss of ASC, but also triggering an unresponsive state.

The plausible involvement of altered stem cells in cancer is another important contribution of the SC field, which suggests the emergence of malignant clones that could evolve and progressively generate a tumor. This is the origin of an SC-centric view of some human diseases. In this line of thought, selective drugs able to cope with cancer stem cells and their metastasis could be a critical step in curing human cancer or rendering it a chronic illness. Development of specific, effective SC-targeted drugs nonetheless requires continued intense effort.

From SC biology to their potential therapeutic use

Asymmetric division capacity is the hallmark of any SC. In the current view, the fundamental SC property of switching between asymmetrical and symmetrical division is controlled by centrosome position and spindle angle in response to cell-to-cell contacts between SC and the stromal cells within the niche. These interactions seem crucial for maintenance of a healthy SC pool, and

altered cell-cell contacts might promote SC evolution towards ageing/senescence/transformation. In this complex landscape, we study a set of proteins in the spindle assembly checkpoint, the machinery responsible for sensing centrosome position and spindle tension, which are likely candidates for coupling spindle orientation to SC fate.

In addition, we try to understand the connections between chromosomal instability and the SC theory of cancer. Most sporadic tumors (85%) develop a combination of genetic defects jointly termed chromosomal instability (CIN). Genome-wide screens have identified a number of potential regulators of SC function, comprised not only of genes with established roles in transcription regulation, cell growth and differentiation, but others whose function is unknown or remains to be validated in the context of SC biology. One of the candidates we study is the Dido locus, a gene complex described in higher vertebrates that encodes three main splice variants, termed Dido1, Dido2 and Dido3[8,9].

The three proteins combine several known domains, including PHD, TF2SM and SPOC. Dido2 and Dido3 have all these domains, but Dido 1 harbors only the PHD domain, which is involved in the recognition of trimethylated histone H3 lysine 4[10]. The Dido3 isoform interacts with centrosomes and the synaptonemal complex in somatic and germ cells, respectively[11,12] Hypomorphic mutations of Dido provoke CIN and increased incidence of hematological myeloid neoplasms in the adult mouse[8], whereas deletion of exon XVI, which encodes the largest part of Dido3, is incompatible with life both in vitro and in mouse models[9,10]. Interestingly, SC generated from targeted deletion of exon XVI show CIN and are unable to differentiate in vitro. To further study the role of Dido in SC and somatic cells, we recently generated mouse models in which Dido3 exon XVI is flanked by LoxP sites. A greater and deeper understanding of SC function is a prerequisite for the definitive development of stem cell therapy.

Expansion of SC in vitro

Human mesenchymal stem cells (hMSC), derived from connective tissues, are a potent tool for a variety of aging-related and autoimmune diseases, and can be considered the current paradigm in cell therapy. Although hMSC can be obtained from several tissues, they are scarce in the body and cell therapy protocols require 10-400 million hMSC per treatment[5]. Ex vivo expansion is therefore necessary. The length of this expansion period and the quality of the cells obtained depend on the isolation and expansion methods used, and are strongly influenced by the patient's clinical history, age and genetic makeup.

All primary cells derived from adults, including hMSC, undergo a limited number of cell divisions in standard culture conditions, where the cell senescence responsible for ageing has a great influence. Although the genetic stability of stem cells is critical for their clinical use, its relationship to SC expansion is poorly understood. We demonstrated that hMSC cultures have a notable percentage of aneuploid cells that increases progressively during standard expansion, until the cultured cells enter a senescent state. This process seems to involve telomere dysfunction and oxidative stress, in association with adaptation of mitochondrial physiology[13]. Comparison to human fibroblasts suggests that the presence of aneuploid cells might be an unavoidable by-product of the in vitro expansion conditions; similar conclusions were recently reported for ESC cultures[14]. We characterised several novel markers associated with the progressive senescence of hMSC, some of which can predict the therapeutic activity of the graft samples[15]. Evolution of these concepts could help to optimise the quality of SC for human therapy.

Homogeneity and reproducibility in Stem Cells populations

One of the lessons learned from the use of ASC in the last ten years is the great variability in results between different research teams and especially between patients. There are many potential sources of variability, but the most obvious is the patient himself, given his unique genetic make-up, life style and medical history, including previous treatment. These factors are obviously expected to have considerable impact on autologous approaches. When feasible, allogeneic settings offer more options for control, and the possibility of transplanting a large preparation of cells from an ideal donor into different patients, thus reducing complexity and variability. Due to the limitations of ASC expansion discussed previously, however, a universal master cell bank cannot yet be generated, and batch-to-batch studies of bioequivalence must be carried out prior to transplant into patients.

From this perspective, the ES and iPS differentiation approach could be extremely useful. This strategy could produce transplantable cells on demand, always from a single certified source (ES, iPS cell line, clone) through a standardised manufacture process. The application of experience from the ASC field will probably provide the best context for full development of ESC potential, reducing or eliminating the current variability attributed to the graft. In addition, automatisation of such a differentiation process could help to reduce costs in a clinical setting.

Stem Cells promises and realities

Many SC sources are being evaluated in hundreds of human clinical trials[5]. Here we will summarise the best examples of promising human SC therapy that use ES or ASC.

Mesenchymal stem cells

MSC are multipotent somatic stem cell precursors of connective tissue, present in the stroma of virtually all mammalian organs. Human MSC have become an increasingly important source for regenerative/reparative medicine, as they can be obtained by minimally invasive techniques, then expanded and differentiated in vitro to different cell lineages. There is growing evidence in animal and in clinical models that administration of ex vivo-expanded MSC has the potential to ameliorate many degenerative disorders, although the molecular mechanisms underlying this therapeutic potential remain largely unknown.

Apart from the potential to provide new differentiated cells, the potent paracrine effector and immunoregulatory capacity of hMSC is now widely accepted, 12 years after their original description[16]. Numerous clinical trials are currently evaluating hMSC for a variety of applications, including immunoregulation, inflammatory and fibrotic diseases, transplant improvement, cardiovascular

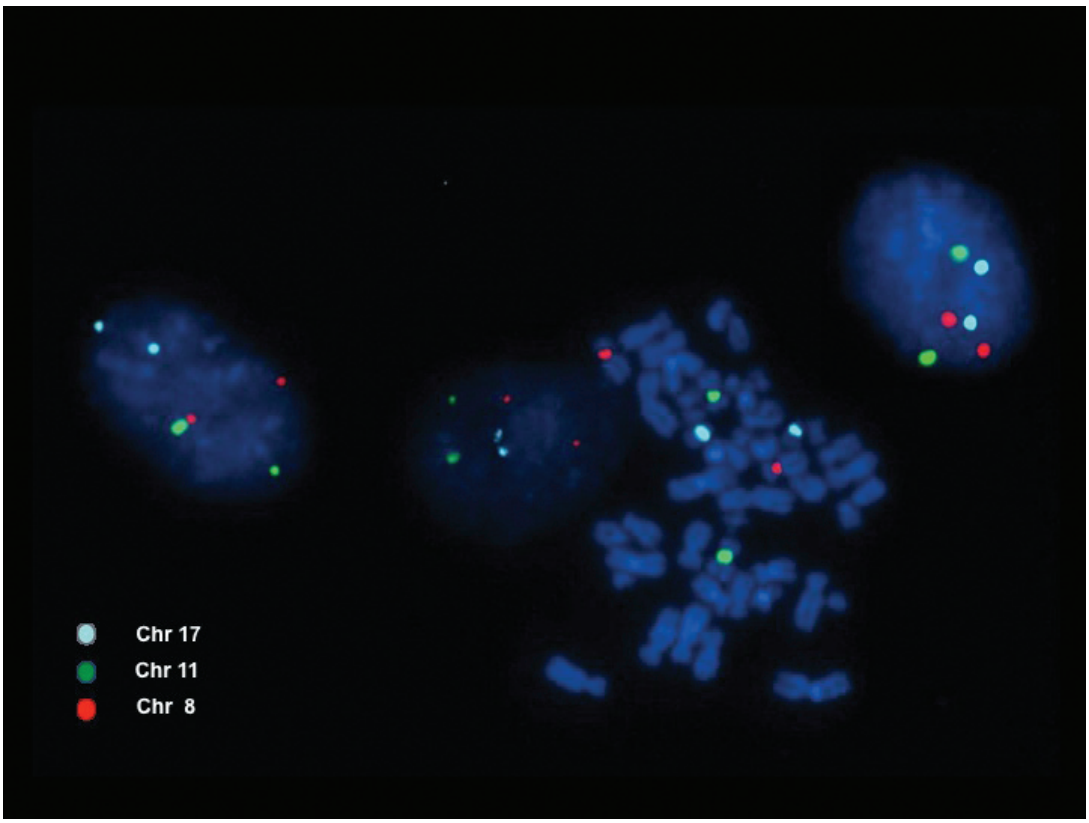

Figure 2. Interphase in situ fluorescent hybridisation with specifc probes for centromeric regions of chromosomes 8, 11 and 17 (labelled in red, green and blue, respectivelly) for aneuploid evaluation in MSC expanded cultures.

disease, and for general or designed-paracrine effects. Despite the large number of such studies, however, the general aspects of hMSC production are still being defined[17]. In summary, the majority of clinical trials have demonstrated the safety of these procedures, with a long follow-up in several cases, but the therapeutic index of the approaches remains low. There is obviously a common or central problem in translating applications from animal models to patients.

Retinal pigmented epithelium (RPE) cells

An organ that has shown more promising results is the retina, with applications for several conditions (AMD, age-related macular degeneration; STGD, Stargardt's disease). Preliminary results include a pilot clinical trial reported in 2012, in which a suspension of dissociated hES-derived RPE (retinal pigmented epithelium) cells were transplanted into two individuals (one with dry AMD and one with STGD).[18] It was suggested that new pigmentation near the injection site in the STGD patient was evidence of RPE function. This multicenter trial is expected to yield additional results shortly. Other clinical tests are evaluating the use of umbilical cord-derived stem cells and hMSC derived from bone marrow or other tissues. The correction of certain pathological conditions of the retina will probably be the first successful example of second-generation cell therapy.

Recent advances in HSC transplant

Allogeneic hematopoietic stem cell (HSC) transplant is a curative treatment for many hematologic malignancies, for which umbilical cord blood (UCB) is an alternative source of HSC. To overcome the low cellularity of a single UCB unit, double UCB transplant has been developed for adults. Initial results suggest double transplant as a promising treatment strategy for some patient groups. In addition, allogeneic UCB has therapeutic potential for cerebral palsy (CP). Preliminary clinical trial results indicate that UCB treatment ameliorated motor and cognitive dysfunction in children with CP undergoing active rehabilitation, accompanied by structural and metabolic changes in the brain[19].

The balance between effectiveness and biosafety in therapeutic use of SC

The initial assumptions that ESC therapies would present greater risk of promoting neoplasms in comparison with relatively safe ASC must probably be revised. ASC are not as inert as anticipated, and evolve significantly when cultured in vitro. Conditions for in vitro expansion must be optimised for each individual SC type, balancing the need for effectiveness against restrictions imposed by the available expansion conditions. For this goal, the development of improved animal models is an unquestionable need. In the last decade, it has become clear that the mouse model, while critically important for answering central questions regarding biology, is a poor indicator of success for a given approach in human clinical therapy[20]. The cause is probably multifactorial, and the proper physiology of the mouse probably is a critical determinant. A second central factor might be associated with the scaling up the procedures. When a response is obtained with 2 x 10^6 cells in a mouse, direct extrapolation would indicate a need for about 200-500 x 10^6 cells in man. The expansion level of the initial cells would thus be larger and probably affect therapeutic capacity. In conclusion, experimental models comprising large (human-sized) animals would be a strict requirement for thorough evaluation before the clinical trial is in place.

A final, important question that is usually forgotten again

comes from the field of hematopoiesis. Bone marrow transplant is probably the first and only cell therapy approach that continues to yield good results, although associated mortality and morbidity remain high. It has long been known that HSC/HPC-containing grafts must be infused with no attempt at expansion. Several attempts claimed to improve HSC self-renewal during ex vivo expansion, but no solution has been translated and standardised for clinical use. In addition, it is routine practice to condition the patient (using chemo- or radiotherapy) to allow engraftment of transplanted cells. Bone marrow engraftment without conditioning has been demonstrated in mice, but requires 100-fold more HSC. It is plausible that current expansion procedures can be improved to preserve or improve therapeutic potential, but some type of intervention would still be needed to generate receptive niches for the transplanted SC or derived cells.

Conclusions

The last 25 years have seen impressive advances in the identification and generation of SC from several organisms. Adult stem cells at first, and subsequently embryonic or induced pluripotent stem cells have been evaluated for their therapeutic potential. Although preliminary results are encouraging, especially with MSC, RPE and HSC, several central aspects of the therapeutic procedure must be optimised to improve the therapeutic index. Preserving the genomic stability of ASC and ESC, intrinsically and after the required expansion, seems particularly important. These observations underline the need for more complete understanding of each SC system. Finally, animal models must undergo critical re-evaluation for each specific intervention, combining previous results with the model's realistic ability to predict SC behavior in man. Despite all these pending technical issues, however, a bright future is envisioned for SC-based therapies. We will see notable improvements and new applications in areas in which no cure is currently available. In addition, the extensive use of ES-derived cells as human disease models will reveal their relevance for drug and toxicology screening, especially in situations where an animal model cannot be substituted. Anti-cancer and immunomodulatory therapies are probably the two areas on which SC-based therapies will have the most direct impact.

REFERENCES

1. Wirth et al. (2013) Gene 525:162-9.
2. Amit et al. (2000) Dev Biol 227:271-8.
3. Birmingham (2003) J Clin Invest 112:458.
4. Takahashi et al. (2007) Cell 131:861-72.
5. www.clinicaltrials.gov.
6. Kelaini et al. (2014) Stem Cell Cloning 7:19-29.
7. Marqués-Torrejón et al. (2013) Cell Stem Cell 12:88-100.
8. Fütterer et al. (2005). J. Clin. Invest 115:2351-2362.
9. Fütterer et al. (2012) Cell Death Differ 19:132-43.
10. Gatchalian et al. (2013). Cell Rep 4:148-58.
11. Sánchez de Diego et al. (2014) Nature Comm 5:4500.
12. Prieto et al. (2009) Chromosoma 118:617-32.
13.Estrada et al. (2013) Cell Death Dis 4:e691.
14.Peterson and Loring (2014) J Biol Chem 289:4578-84.
15.Sepúlveda et al. (2014) Stem Cells. doi: 10.1002/stem.1654.
16. Di Nicola et al. (2012) Blood 99:3838-43.
17. Nystedt et al. (2013) Stem Cells 31:317-26.
18. Schwartz et al. (2012) Lancet 379:713-20.
19. Min et al. (2013) Stem Cells 31:581-91.
20. Mak et al. (2014) Am J Transl Res 6:114-8.

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BIOGRAPHY OF DR. KAREL VAN WELY

Karel H.M. van Wely (Uden, the Netherlands, 1970), studied biomedical sciences at the University of Utrecht, where he obtained his B.Sc. degree in 1993. He then moved to the Univeristy of Groningen to work on protein secretion in Bacillus subtilis, a bacterium with a widespread application in industrial enzymes. He defended his Ph.D. thesis on this subject in the year 2000, after which he turned his interest to oncology and myeloid differentiation. A postdoctoral stage at the Erasmus University in Rotterdam was completed in 2002, at which time he moved to Spain and the Centro Nacional de Biotecnología. Apart from his work on the characterisation of non-canonical gene functions in cancer, he has a general interest for carcinogenesis and chromosomal instability. A line of research specifically dedicated to the role of the mitotic spindle in chromosome breakage was initiated a few years after his move to Spain, when a small taskgroup on this topic was assembled. Karel van Wely has obtained several scholarships from regional and national agencies to fund his position and research at the CNB, and has produced a steady flow of publications on his research interests including two books for the general public.

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Antonio Bernad (Zaragoza 1961) obtained the master in Chemical Sciences by Universidad Autónoma de Madrid, in Biochemistry and Molecular Biology (1984). He obtained his PhD (1989) at the Centro de Biología Molecular Severo Ochoa (Madrid). From 1990 to 1993 he worked as a Senior Researcher in the Department of Biological Effects at the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT) in Madrid, where he established techniques for somatic gene transfer to hematopoietic stem cells. In 1993 he was an invited researcher at the Center for Blood Research at Harvard Medical School, and, in 1994, he joined the Centro Nacional de Biotecnología (CNB.Madrid) as senior track researcher of the Consejo Superior de Investigaciones Científicas (CSIC). At the CNB, first in the Department of Molecular Biology and later in the Department of Immunology and Oncology (DIO), he built a research team focused on the biology of hematopoietic and mesenchymal stem cells and their use for tissue engineering. In 2006 he was promoted to CSIC Full Professor and in 2007 he moved his group to the National Center for Cardiovascular Research (CNIC), as Director of the Regenerative Cardiology Department. There, he has been highly committed with the fields of adult cardiac stem cells (CSC) and their regulation in homeostasis, and biosafety on cell therapy. Currently he is back DIO (CNB.CSIC) and coordinator of the European project CARE-MI, focused in the clinical evaluation of CSC in allogeneic transplant.

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